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Synthetic studies directed toward the total synthesis of dolabriferol☆

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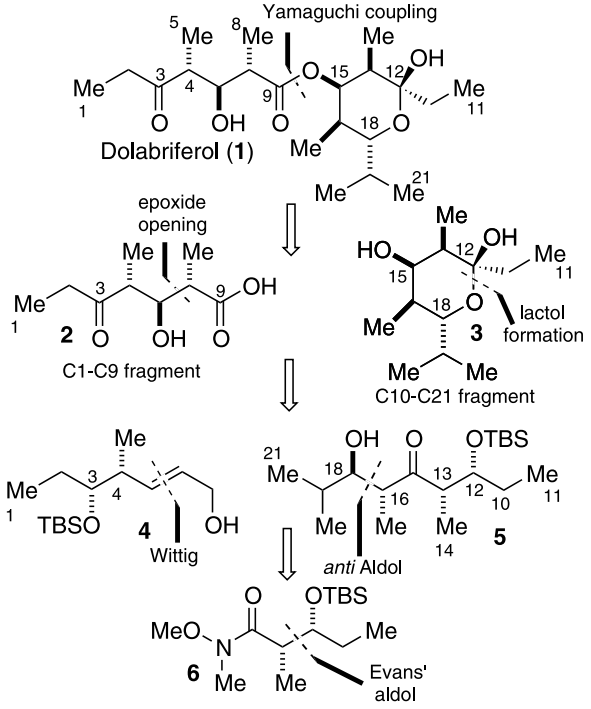
This paper is dedicated to Professor Albert Kascheres on the occasion of his 60th birthday and also to the Brazilian Chemical Society (SBQ)

Abstract—Herein we report our results towards the total synthesis of (–)-dolabriferol, describing the synthesis of fragments C1–C9 and C10–C21. This convergent asymmetric approach relies on the use of a common Weinreb amide precursor for the preparation of both fragments, an efficient *anti*-aldol reaction followed by $Zn(BH_4)_2$ reduction to give a 1,3-*syn* diol, a selective oxidation of a triol under Swern conditions with concomitant lactol formation, and a diastereoselective epoxidation of an allylic alcohol with *m*-CPBA followed by an efficient epoxide opening with $Me_2CuCNLi_2$.

Opisthobranchs are gastropod mollusks barely protected by a small and fragile shell, internal or completely absent. Very often these mollusks are chemically armed against potential predators and many studies have proven the presence of distasteful molecules in the skin and in the mucous secretion of these animals. In the first reported natural product investigation of the opisthobranch mollusk family *Dolabriferidae*, the polypropionate dolabriferol (**1**) was isolated from parapodia of the Cuban anaspidean mollusk *Dolabrifera dolabrifera*.[1] The structure and the relative stereochemistry of dolabriferol were determined by X-ray analysis, while the absolute configuration has not previously been established. The non-contiguous carbon skeleton of **1** is unusual in polypropionate metabolites.[2] This was the first reported natural product investigation of the opisthobranch mollusk family *Dolabriferidae* and suggests that this family may also prove to be a good source of new polypropionate metabolites.

To determine the absolute configuration of dolabriferol, and to provide material for biological studies, we initiated a project directed towards its total synthesis. The convergent approach described here might provide access to dolabriferol and additional derivatives with potential relevance to biological studies.

Not surprisingly, our first disconnection, summarized in Scheme 1, involved cleavage of the ester bond to give keto acid **2** (C1–C9 fragment) and hemiketal **3** (C10–C21 fragment).[3] The synthetic analysis involved the opening of hemiketal **3** to give an acyclic precursor **5**



Scheme 1.

☆ Supplementary data associated with this article can be found at doi:10.1016/S0040-4039(03)01351-0

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bearing four stereogenic centers, prepared from the Weinreb amide precursor **6**.

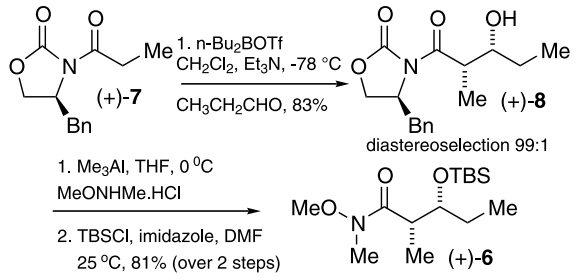
Of the available options, we speculate that the desired C13 and C16 methyl bearing stereocenters in **5** might be established through a boron enolate mediated aldol reaction and that the derived *anti–syn* aldol might be transformed into the desired stereochemical array through $Zn(BH_4)_2$ reduction.[3]

The TBS-protected alcohol functionality at C12 in **5** should be converted to a ketone to enable hemiketal formation with the OH-functionality at C18 at a late stage. The acyclic side chain **2** is viewed as arising from an allylic alcohol **4** by selective epoxidation followed by epoxide opening with $Me_2CuCNLi_2$.

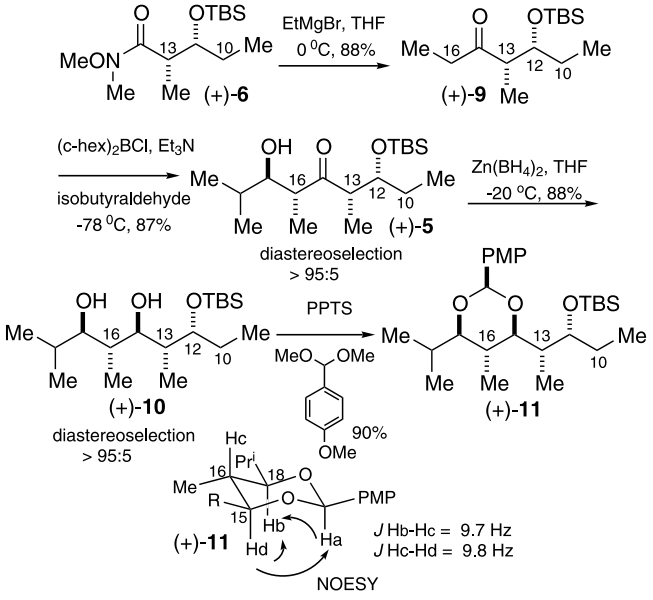
The allylic alcohol **4** may be further dissected in a straightforward manner to give amide **6**. Again, the OTBS function at C3 in **4** should be transformed to a carbonyl group in segment C1–C9. It is noteworthy that both segments could be obtained from the common Weinreb amide intermediate **6**, and that the same OTBS functionality in **6** should be converted to a ketone late in the synthesis of both fragments.

Synthesis of fragment C10–C21 began with the known acyloxazolidinone (+)-**7**, which was most conveniently prepared by acylation of the corresponding (−)-(*S*)-oxazolidinone (Scheme 2).[4] Asymmetric aldol addition of the boron enolate derived from oxazolidinone (+)-**7** with propionaldehyde gave the aldol adduct (+)-**8** in 83% yield and 99:1 diastereoselectivity (Scheme 2).[5]

Subsequent protection of the alcohol functionality as its TBS ether cleanly provided the Weinreb amide (+)-**6**, a versatile intermediate, common to the synthesis of both fragments, in 81% yield (over two steps).[6,7] Ethylmagnesium bromide addition to the Weinreb amide (+)-**6** gave the corresponding ethylketone (+)-**9** in 88% isolated yield (Scheme 3).[8,9] Selective generation of the (*E*)-enol dicyclohexylborinate by treatment of the ethyl ketone (+)-**9** with $(c\text{-hex})_2BCl$ and Et_3N followed by addition of isobutyraldehyde provided the desired aldol product (+)-**5** in greater than 95% diastereomeric purity (87% yield).[10] Chelate-controlled selective reduction of (+)-**5** to yield the *syn* 1,3-diol (+)-**10** was achieved through the use of $Zn(BH_4)_2$ (88% yield, >95:5 diastereoselection).[11]



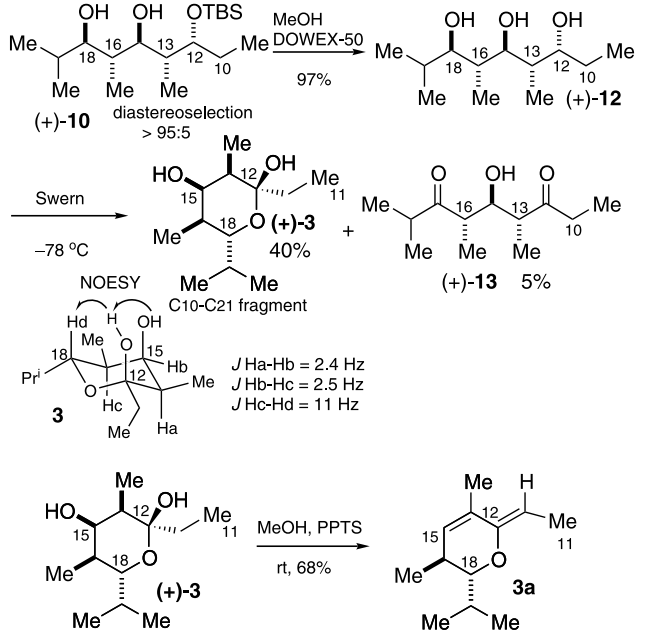
Scheme 2.



Scheme 3.

To confirm the relative stereochemistry of the aldol bond construction and the reduction steps, 1,3-diol (+)-**10** was converted to its *p*-methoxybenzylidene acetal (+)-**11** (90% yield). The illustrated NOESY interactions between Ha, Hb and Hd, together with the large vicinal coupling constants between Hb–Hc (9.7 Hz), and Hc–Hd (9.8 Hz), unambiguously establish the proposed relative stereochemistry (Scheme 3).[12]

Removal of the TBS protecting group at C12 in (+)-**10** was accomplished by treatment with MeOH in the presence of Dowex-50, leading to triol (+)-**12** in 97% yield (Scheme 4).[3] We were gratified to see that treatment of triol (+)-**12** under controlled Swern oxidation



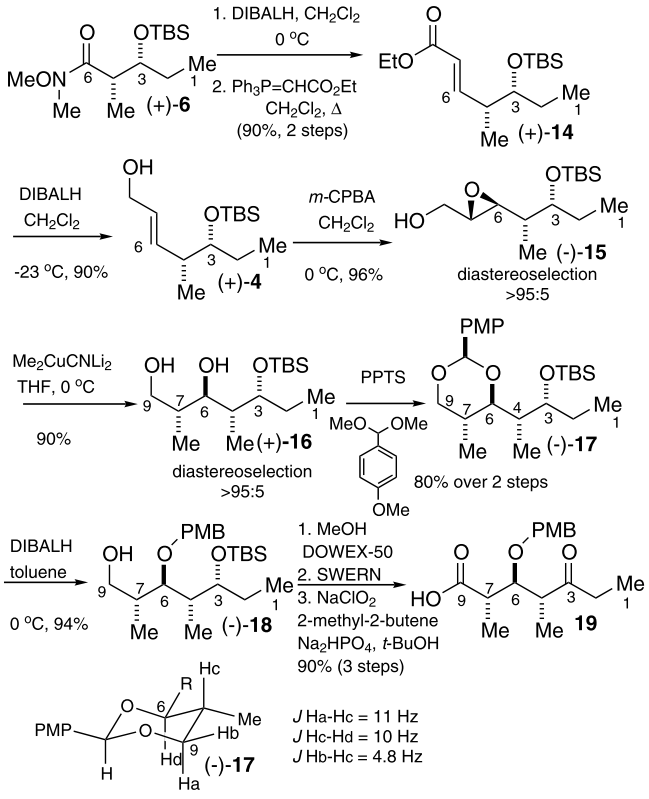
Scheme 4.

conditions at −78°C, gave the desired lactol (+)-**3** in 40% isolated yield.[13] We have observed formation of lactol (+)-**3** (40%) and diketone (+)-**13** (5%) together with recovered starting material (50%) as the only detectable compounds.[13] The very stable lactol (+)-**3**, diketone (+)-**13** and starting material (+)-**12** could be separated by silica gel flash column chromatography. Of the three OH functions in triol (+)-**3** we observed a preference for oxidation at the less hindered position at C12 which cyclized with the OH function at C18 to give (+)-**3** in a very clean reaction. To the best of our knowledge, this is the first example of selective oxidation of a triol described in the literature. At this point, the relative stereochemistry for fragment C10–C21 was established by the illustrated NOESY interactions as well as by coupling constant analysis in the ^{1}H NMR spectra of (+)-**3** (Scheme 4). The large vicinal coupling constant between Hc–Hd (11 Hz), together with the small observed values for Ha–Hb (2.4 Hz) and Hb–Hc (2.5 Hz) unambiguously establish the proposed relative stereochemistry. The eight-step sequence starting from (+)-**7** proceeded in 17% overall yield.

At this stage, we tried to prepare the corresponding methyl-lactol in order to carry out the necessary coupling reaction between the two fragments (Scheme 4). Unfortunately, treatment of lactol (+)-**3** with PPTS in MeOH gave diene **3a** as the major product, in 68% isolated yields. We learned that lactol (+)-**3** is also very acid sensitive and prone to decomposition. Aldol adduct (+)-**5**, easily prepared in gram quantities (Scheme 3) was kept as a storage point for material on the basis that it still allows for variations in strategy if the proposed coupling reaction did not proceed as planned.

Our approach for preparation of fragment C1–C9 was also initiated with the Weinreb amide (+)-**6** (Scheme 5). This amide was smoothly reduced to the aldehyde on treatment with diisobutylaluminum hydride at 0°C.[7] This unpurified aldehyde was directly subjected to a Wittig homologation with the requisite stabilized ylide reagent to give α,β-unsaturated ester (+)-**14** in 90% isolated yield over the two-step sequence.[14,15] Reduction of (+)-**14** with 2.2 equivalents of diisobutylaluminum hydride at −23°C gave allylic alcohol (+)-**4** (90% yield).[14] Epoxidation of allylic alcohol (+)-**4** with *m*-CPBA proceeded with complete stereoselectivity from the opposite side of the C3 *tert*-butyldimethylsilyl group to yield the *anti*-epoxy alcohol (−)-**15** as a single product in high purity (96% yield).[16] It is noteworthy that the diastereoselectivity associated with this epoxidation was exceptional and compared in both yield and selectivity to related transformations described earlier by Isobe et al. and later on by Miyashita et al.[16]

Epoxide opening proceeded smoothly with high regioselectivity after treatment of the epoxy alcohol (−)-**15** with $Me_2CuCNLi_2$ to give diol (+)-**16** in good yield and selectivity, which possesses *anti–anti–syn* stereochemistry for the four contiguous stereocenters.[17] Formation of *p*-methoxybenzylidene acetal (−)-**17** was accomplished by treatment of the corresponding diol



Scheme 5.

with *p*-methoxybenzaldehyde dimethyl acetal and a catalytic amount of PPTS (80% yield, over two steps). The use of CSA, instead of PPTS in this reaction, gave the secondary alcohol with loss of the TBS protecting group at C3. The stereochemical outcome of the epoxide opening was determined by coupling constant analysis in the ^{1}H NMR spectra of benzylidene acetal (−)-**17**. The large vicinal coupling constants between Ha–Hc (11 Hz) and Hc–Hd (10 Hz) together with the small observed value between Hb–Hc (4.8 Hz) unambiguously established the proposed 1,2-*anti* relative stereochemistry between C6 and C7 in *p*-methoxybenzylidene acetal (−)-**17** (Scheme 5).

Selective DIBALH-mediated acetal cleavage in (−)-**17** gave the desired *p*-methoxybenzyl ether alcohol (−)-**18** in 94% yield with complete regioselectivity (Scheme 5).[18] A three-step sequence involving removal of the secondary TBS protecting group at C3, careful Swern oxidation under standard conditions,[13] followed by treatment of the intermediate aldehyde with $NaClO_2$, gave the desired carboxylic acid **19** in 90% overall yield.[19] The 13-step sequence from (+)-**7** to **19** proceeded in an overall yield of 32% and was amenable to a gram scale-up.

In conclusion, the synthesis of both fragments of (−)-dolabriferol has been described.[20] Notable features of this approach include double convergence, with each of the two advanced segments derived from a common Weinreb amide precursor, an efficient *anti* aldol reaction followed by $Zn(BH_4)_2$ reduction to the 1,3-*syn* diol, a selective oxidation of a triol under Swern conditions,

with concomitant lactol formation, and a diastereoselective epoxidation of an allylic alcohol, followed by epoxide opening with $Me_2CuCNLi_2$.

Although this approach provides lactol (+)-**3** and carboxylic acid **19** in sufficient quantity to support the total synthesis and allow coupling studies at a later time, further optimization, especially in order to improve the oxidation/cyclization sequence from triol (+)-**12** to lactol (+)-**3**, is still required.[20] Progress toward the total synthesis continues and will be reported in due course.

Supporting information

The following supporting information is available on line: Spectral data for key intermediates.

Acknowledgements

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